

## PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—A61k. C07c.

## COMPLETE SPECIFICATION

## Steroids and Biologically Active Preparations Containing Steroids

We, ORGANON LABORATORIES LIMITED, a British Company, of Brettenham House, Lancaster Place, London, W.C.2, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

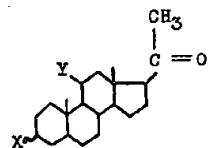
5 The invention relates to the manufacture of new biologically active preparations which have a depressor effect on the central nervous system, to new water soluble compounds of the pregnane series with the said activity, and to the preparation thereof.

10 It is known that steroids which have a hormone activity may in some cases at the same time have an anaesthetic activity. For example, in Proc. Soc. Exper. Biol. and Med. 46, 116 (1941), H. Selye describes some steroids which, when administered to mice and rats, have a narcotising action. A disadvantage of the use of these steroids is that, among other things on account of their hormone activity, they may give rise to an 15 undesired side effect. Another disadvantage is that, owing to their poor solubility in the commonly used injection media, they cannot be administered intravenously. On intraperitoneal administration it appears in 20 addition that the anaesthetically active dose of, for example progesterone and desoxycorticosterone, is of the same order of magnitude as the lethal dose.

25 In J. Amer. Med. Ass. 158, 1412 (1955), F. J. Murphy c.s. describe the sodium succinate of the 21-hydroxy-3:20-dioxo-pregnane which has an anaesthetic activity. This compound has the advantage that it is 30 reasonably soluble in an aqueous medium, so that it can be administered intravenously. Clinical investigations have, however, shown that in a large number of cases application of this substance results in thrombo-phlebitis and phlebothrombosis (see The 35 Lancet, Vol. 270, June, 1956, page 1002). On

account of the restricted mode of administration of the known anaesthetically active steroid compounds and the undesired side phenomena occurring on application of these compounds, the need remained for other compounds which can be applied as anaesthetics in various modes of administration and which, on application do not cause an undesired effect.

50 A process has been found for the manufacture of preparations which have a depressor effect on the central nervous system, characterised in that a compound of the pregnane or alopregnane series of the general formula:



wherein

55 X represents an oxo or an  $\alpha$ - or  $\beta$ -hydroxyl group, or an  $\alpha$ - or  $\beta$ -acyloxy group derived from a monocarboxylic acid containing from 1 to 10 carbon atoms, or an  $\alpha$ - or  $\beta$ -acid acyloxy group derived from a polycarboxylic acid containing from 2 to 8 carbon atoms, and the alkali-metal, ammonium and substituted ammonium salts of these polycarboxylic acid esters, and

60 Y represents an oxo- or  $\beta$ -hydroxyl group, is combined with a pharmaceutical carrier which is inert to the active substituent, harmless to human beings, and is suitable for oral or parenteral administration.

65 Dependent on the dosage and the mode of administration, these preparations may have an anaesthetic, hypnotic, sedative, and anti-convulsive effect, occurring separately or simultaneously.

70 Preferably the following steroids may be applied as active constituents:

[Price 3s. 6d.]

Price 25

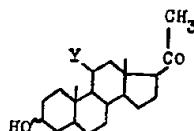
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5      3:11:20-tri-oxo-pregnane;  
       3:11:20-tri-oxo-allo-pregnane;  
       3 $\alpha$ -hydroxy-11:20-dio-oxo-pregnane;  
       3 $\alpha$ -hydroxy-11:20-dio-oxo-allo-pregnane;  
       5      3 $\beta$ -hydroxy-11:20-dio-oxo-allo-pregnane;  
       3 $\alpha$ :11 $\beta$ -dihydroxy-20-oxo-pregnane;  
       3 $\beta$ :11 $\beta$ -dihydroxy-20-oxo-pregnane.

Not only the above compounds, but also 10 functional derivatives thereof, in which the 3-hydroxyl group has been converted into the ester group may be applied as active constituent.

These esters are derived from aliphatic, 15 aromatic, or araliphatic monocarboxylic acids, having from 1—10 carbon atoms such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, oenanthic acid, caprylic acid, crotonic acid,  $\beta$ -cyclopentylpropionic acid,  $\gamma$ -cyclohexylbutyric acid, chloracetic acid, trifluoracetic acid, trimethyl acetic acid, di-ethyl acetic acid, carbamic acid, glycine, alanine, serine, leucine, benzoic acid, phenyl acetic acid,  $\beta$ -phenyl propionic acid, furane-2-carboxylic acid, and isonicotinic acid.

In addition it was found that as active 20 constituents in the present preparations new 3-acid polycarboxylic esters of pregnane or allo-pregnane compounds are preferably applied 25 of the formula:



in which:

Y represents an oxo- or  $\beta$ -hydroxyl group 35 and which esters are derived from polycarboxylic acids containing 2—8 carbon atoms.

As examples of the polycarboxylic acids 40 which may be applied in the preparation of the active derivatives are mentioned: malonic acid, succinic acid, glutaric acid, pimelic acid, fumaric acid, maleic acid, malic acid, tartaric acid, citric acid, aconitic acid, tricarballylic acid, aspartic acid, glutamic acid and phthalic acid. The use of succinic acid has 45 appeared of advantage.

In the formation of the acid esters of the 50 present steroids, for example, the hemisuccinates, preferably an excess of acid anhydride is applied, for example, succinic anhydride. It is customary to apply pyridine as a solvent. The ester formation takes place already at room temperature.

Finally it was found that the alkali metal, 55 ammonium and substituted ammonium salts of the new 3-acid polycarboxylic esters of the said pregnane and allo-pregnane compounds

not described in the literature before, likewise have a depressor effect on the central nervous system and can be applied as active constituent in the present preparations. Especially on account of their good solubility, the said salts are extremely suitable for intravenous administration. The alkali metal salts are highly soluble, for example, the potassium and sodium salts, the ammonium salt and the substituted ammonium salts of the said acid polycarboxylic esters. The latter salts are ammonium salts, in which one or more hydrogen atoms connected with the nitrogen have been replaced by a possibly substituted alkyl, aryl, or aralkyl group. As examples of such compounds which may be used in the formation of the salts, are mentioned: dimethylamine, trimethylamine, diethylamine, triethylamine, diethanolamine, dimethylethanolamine, dimethylbenzylamine, N:N'-tetramethyl-hexamethylene-diamine, procaine, and Xylocaine (Registered Trade Mark).

The preparation of the salts of the aforesaid 60 3-acid polycarboxylic esters takes place, for example, by dissolving, in an aqueous liquid, an acid ester together with an equivalent quantity of a base, for example, sodium bicarbonate or sodium hydroxide, as a result of which the desired salt is formed. If desired, the salt can be obtained from the solution as a solid substance by lyophilization.

The present preparations in which the 65 steroid compounds occurring as active constituents have no hormone activity, have a number of important advantages in regard to the known anaesthetically active steroid compounds.

First of all, at a relatively low dosage, these 70 preparations show a strongly anaesthetic activity. Secondly, the steroid compounds applied are very rapidly taken up by the intestine, as a result of which the present preparations are at the same time suitable to be orally administered. An important advantage of the oral mode of administration lies in the exclusion of the occurrence of thrombo-phlebitis.

It has appeared that some of the present 75 steroids, after administration in a very low dosage, have a hypnotic effect, so that they may also be applied as hypnotics.

In addition it has appeared that some of the present steroids have a sedative effect and/or are capable of inhibiting the effect of 80 the cardiazol, and consequently have an anti-convulsive effect.

The present preparations may be administered 85 both orally, for example, in the form of tablets, pills, and coated tablets, rectally, for example, in the form of suppositories, and intramuscularly or intraperitoneally, for example, in a suspended form.

The salts of the polycarboxylic esters described herein dissolved in an aqueous solu- 90

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tion suitable for injection, are suitable for intramuscular, intraperitoneal and intravenous administration. These aqueous solutions are characterised by their rapid action after the administration. When manufacturing these preparations naturally the auxiliary substances commonly used for injection preparations may be applied, for example, a compound to render the solution isotonic, for example, such as sodium chloride and glucose, and an anti-septic. If the chance of thrombophlebitis occurring on intravenous administration is present, cortisone or hydrocortisone is added to these solutions in a quantity amounting to about 10% of the other steroids present, as a result of which this undesired side phenomenon does not occur.

In the manufacture of the preparations destined for oral administration use is made, for example, of filling substances, such as lactose, a disintegrating agent, such as starch, a lubricant, such for example as talc and magnesium stearate, and, if necessary, also taste-modifying agents and dyes. A mass so obtained can be readily pressed to tablets.

Pharmacological experiments regarding the depressor effect on the central nervous system demonstrated that oral or intraperitoneal administration to mice of  $3\alpha$ -hydroxy-11:20-dioxopregnane and of  $3\alpha:11\beta$ -dihydroxy-20-oxopregnane in a quantity of 100 mg. per kg. body weight gives a very rapid and prolonged narcotizing effect. In addition it has appeared that the lethal dose of these preparations is very high.

Intravenous administration to mice and rabbits of an aqueous solution of the sodium salt of  $3\alpha$ -hydroxy-11:20-dioxopregnane-3-hemisuccinate in a quantity of 50 mg. of salt per kg. body weight resulted in narcosis.

The following examples serve to illustrate the manufacture of preparations with the present steroids as active constituents and show various modes of administration, as well as the preparation of acid polycarboxylic esters of the steroids in question and the water soluble salts derived therefrom, which may be applied as active constituents in the present preparations.

#### EXAMPLE I.

By means of 1.5 gm. of gelatin a granulate is prepared of 186 gm. of lactose. The mass is thoroughly dried, after which 25 gm. of  $3\alpha$ -hydroxy-11:20-dioxo-alloregnane, 25 gm. of amyum, and 12.5 gm. of talc are added. After mixing the mass is pressed to 250 mg. tablets.

#### EXAMPLE II.

50 gm. of  $3\alpha$ -hydroxy-11:20-dioxopregnane-3-citrate are dissolved in sufficient 1 N sodium hydroxide solution until the solution has a pH of 8. Then the solution is lyophilised in vacuo, after which the resulting Na-salt is dissolved in 1000 ml. of a 0.9% sodium chloride solution in water. This solu-

tion is suitable for injection.

#### EXAMPLE III.

50 gm. of 3:11:20-trioxopregnane and 50 gm. of 3:11:20-tri- $\alpha$ -alloregnane are mixed with 1960 gm. of lactose and 270 gm. of potato starch. Then a solution of 30 gm. of gelatin in 180 ml. of distilled water is added and then a solution of 30 gm. of potato starch in 360 ml. of distilled water. The mass is thoroughly mixed and then dried. Subsequently 450 gm. of amyum, 140 gm. of talc, and 20 gm. of magnesium stearate are added to this substance, after which this mixture is pressed to tablets of 150 mg. each.

#### EXAMPLE IV.

5 gm. of  $3\alpha:11\beta$ -dihydroxy-20-oxopregnane are rolled in a ball-mill with 50 ml. of water until the crystals are smaller than 50  $\mu$ . Then 2 gm. of polyoxyethylene-sorbitan-monolaurate (Tween 20 [Registered Trade Mark]), a solution of 5 gm. of carboxymethyl cellulose in 500 ml. of water, 3 gm. of  $Na_2HPO_4$  and 11.5 gm. of  $NaH_2PO_4$  dissolved in 300 ml. of water, and finally 10 ml. of benzyl alcohol are added to the suspension thus obtained, after which the suspension is completed with water to 1000 ml. The suspension thus obtained can be administered intramuscularly or intraperitoneally.

#### EXAMPLE V.

5 gm. of 3:11:20-trioxopregnane are dissolved, while heating, in a mixture of 100 ml. of benzyl alcohol and 900 ml. of arachis oil. The oily solution thus obtained is suitable for intramuscular injection.

#### EXAMPLE VI.

In accordance with the methods of examples I-V, tablets, solutions, and suspensions have been prepared, containing as active constituents acid polycarboxylic esters, notably, the 3-hemisuccinate, the 3-hemiglutamate, the 3-hemitartrate, and the 3-acid-citrate of  $3\alpha$ -hydroxy-11:20-dioxopregnane,  $3\alpha$ -hydroxy-11:20-dioxo-alloregnane,  $3\beta$ -hydroxy-11:20-dioxo-alloregnane,  $3\alpha:11\beta$ -dihydroxy-20-oxopregnane and  $3\beta:11\beta$ -dihydroxy-20-oxopregnane.

#### EXAMPLE VII.

In accordance with the processes of examples I-V, tablets, coated tablets, pills, and solutions—suitable for oral, rectal, intramuscular, intraperitoneal and intravenous administration—have been prepared from the sodium, potassium, ammonium salts and from some substituted ammonium salts, viz., the dimethylamine, the dimethylethanolamine, and the dimethylbenzylamine salts of the acid polycarboxylic esters mentioned in example VI.

The solutions destined for intravenous administration were in addition mixed with a quantity of 10% by weight of cortisone and/or hydrocortisone in regard to the quantity of ester salt applied.

## EXAMPLE VIII.

14 gm. of  $3\alpha$ -hydroxy-11:20-dioxo-pregnane are dissolved in 180 ml. of pyridine. To the solution 20 gm. of finely pulverized succinic anhydride are added. After 24 hours the reaction mixture is poured into 1.5 l. of icy water. The excess of pyridine is neutralized with hydrochloric acid, the resulting precipitate consisting of the hemisuccinate of the steroid is filtered and washed with water.

By crystallisation from isopropylether the pure  $3\alpha$ -hydroxy-11:20-dioxo-pregnane-3-hemisuccinate is finally obtained with a m.p. of 172—173° C. ( $\alpha$ )<sub>D</sub> = +119° (dioxane).

## EXAMPLE IX.

A mixture of 15 gm. of the dry  $3\alpha$ -hemisuccinate of  $3\alpha$ -hydroxy-11:20-dioxo-pregnane and 3.146 gm. of sodium bicarbonate is dissolved in 250 ml. of water. The solution is lyophilized in vacuo, as a result of which the sodium salt of the  $3\alpha$ -hydroxy-11:20-dioxo-pregnane-3-hemisuccinate is obtained.

## EXAMPLE X.

10 gm. of  $3\alpha:11\beta$ -dihydroxy-20-oxo-pregnane are dissolved in 150 ml. of pyridine. To this solution 14 gm. of powdered succinic anhydride are added, after which the mixture is left to stand for 24 hours. Subsequently it is poured out into 1 l. of icy water and the excess of pyridine is neutralized with hydrochloric acid. The resulting precipitate, consisting of the  $3\alpha$ -hemisuccinate of  $3\alpha:11\beta$ -dihydroxy-20-oxo-pregnane, is filtered, washed with water, and dried. Then the hemisuccinate is dissolved in water together with an equivalent quantity of sodium bicarbonate and the solution is lyophilized in vacuo, as a result of which the sodium salt of the  $3\alpha:11\beta$ -dihydroxy-20-oxo-pregnane-3-hemisuccinate is obtained.

## EXAMPLE XI.

To a solution of 14 gm. of  $3\alpha$ -hydroxy-11:20-dioxo-pregnane in 175 ml. of pyridine are added 15 gm. of glutaric acid anhydride. The resulting mixture is heated under reflux for about 1 hour, after which the reaction mixture is poured into 1.5 l. of icy water. The aqueous solution is acidified to a pH of 3 with dilute hydrochloric acid and extracted with ether. The ether extract is then washed with water and dried over sodium sulphate. After evaporation of the ether crystalline  $3\alpha$ -hydroxy-11:20-dioxo-pregnane-3-hemiglutamate is obtained.

## EXAMPLE XII.

In an analogous manner as described in example XI other acid esters have been prepared from the  $3\alpha$ -hydroxy-11:20-dioxo-pregnane by replacing the glutaric anhydride by an equivalent quantity of maleic anhydride—viz., the hemimaleate and hemifumarate and in addition the hemitartrate and the acid-citrate by making use of tartaric acid anhydride and citric acid anhydride respectively.

## EXAMPLE XIII.

A mixture of 1 gm. of the hemiglutamate of  $3\alpha$ -hydroxy-11:20-dioxo-pregnane and 0.23 gm. of potassium bicarbonate is dissolved in 25 ml. of water. The solution is lyophilised in vacuo, as a result of which the potassium salt of the  $3\alpha$ -hydroxy-11:20-dioxo-pregnane-3-hemiglutamate is obtained.

## EXAMPLE XIV.

Following the procedure described in example XIII some other salts have been prepared from the acid esters described in examples XI and XII, viz., the sodium salt, the ammonium salt, and the salts derived from trimethylamine, diethanolamine, and dimethylbenzylamine.

## EXAMPLE XV.

10 gm. of  $3\alpha:11\beta$ -dihydroxy-20-oxo-pregnane are dissolved in 150 ml. of pyridine. To this solution 20 gm. of citric anhydride are added, after which the mixture is heated under reflux for 2 hours.

To the resulting reaction mixture is then added 1 l. of icy water and the excess of pyridine is neutralised with hydrochloric acid. The resulting precipitate is filtered, washed with water, and dried, as a result of which the 3-acid-citrate of  $3\alpha:11\beta$ -dihydroxy-20-oxo-pregnane is obtained.

## EXAMPLE XVI.

In an analogous manner to that described in example XV the following acid esters of  $3\alpha:11\beta$ -dihydroxy-20-oxo-pregnane have been prepared by replacing the citric anhydride by the respective acid anhydrides: the 3-hemiglutamate, the 3-hemipimelate, and the 3-hemitartrate. According to the process of example IX these acid esters have been converted into the sodium, potassium, and ammonium salts and into the salts derived from the dimethylamine, N:N<sup>1</sup>-tetramethyl hexamethylenediamine.

## EXAMPLE XVII.

2 gm. of  $3\alpha$ -hydroxy-11:20-dioxo-allo-pregnane are dissolved in 30 ml. of pyridine. To this solution are added 2 gm. of succinic acid anhydride. After 20 hours the reaction mixture is poured into 200 ml. of icy water. The aqueous solution is acidified with dilute hydrochloric acid and extracted with 50 ml. of ether. The ether extract is dried over magnesium sulphate. After evaporation of the ether  $3\alpha$ -hydroxy-11:20-dioxo-allo-pregnane-3-hemisuccinate is obtained.

In an analogous manner some other acid esters have been prepared from the  $3\alpha$ -hydroxy-11:20-dioxo-allo-pregnane, viz., the 3-hemisuccinate, the 3-hemipimelate, the 3-hemimaleate, and the 3-acid-citrate.

## EXAMPLE XVIII.

Entirely in accordance with the process described in example IX, the acid esters mentioned in example XVII have been converted into the sodium, potassium, and ammonium

salts and into the salts derived from the trimethylamine, diethanolamine, and dimethylbenzylamine.

EXAMPLE XIX.

5 To a solution of 1 gm. of  $3\beta:11\beta$ -dihydroxy-20-oxo-pregnane—melting at  $255^{\circ}$  C.—in 15 ml. of pyridine are added 1.2 gm. of powdered succinic anhydride. The resulting mixture is heated on the steam bath under 10 reflux for 1 hour. The reaction mixture is then poured into 200 ml. of icy water. The aqueous solution is neutralised with dilute hydrochloric acid, the resulting precipitate consisting of the 3-hemisuccinate of  $3\beta:11\beta$ -dihydroxy-20-oxo-pregnane is filtered and 15 washed with water.

According to the above process also other acid esters have been prepared from the  $3\beta:11\beta$ -dihydroxy-20-oxo-pregnane, viz.: the 20 3-hemiglutamate, the 3-hemisuberate, the 3-hemimalate, the 3-acid-citrate, the 3-hemiphthalate, and the 3-hemiaspartate.

EXAMPLE XX.

25 The acid esters mentioned in example XIX have, entirely in accordance with the process described in example IX, been converted into the sodium, potassium, and ammonium salts. From the 3-hemisuccinate and the 3-citrate the salts derived from diethylamine, dimethylethanolamine and dimethylbenzylamine have in addition been prepared.

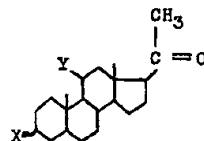
EXAMPLE XXI.

35 Following the procedure described in example XIX the 3-hemisuccinate of  $3\beta$ -hydroxy-11:20-dioxo-allopregnane has been prepared which acid ester has then been converted into the sodium, potassium, and ammonium salts and into the salts derived from dimethylamine, dimethylbenzylamine, and diethanolamine.

In an analogous manner the acid esters of the  $3\beta$ -hydroxy-11:20-dioxo-allopregnane have been prepared of glutaric acid, 45 tartaric acid, and citric acid. Of the latter acid esters the sodium, potassium, and ammonium salts have been prepared according to the process described in example IX and the salts derived from triethylamine, dimethylethanolamine, and N:N<sup>1</sup>-tetramethylhexamethylenediamine.

WHAT WE CLAIM IS:—

1. Process for the manufacture of preparations which have a depressor effect on the central nervous system, characterised in that a compound of the pregnane or allopregnane series of the general formula:



wherein

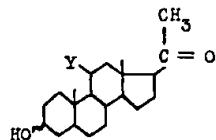
X represents an oxo- or an  $\alpha$ - or  $\beta$ -hydroxyl group, or an  $\alpha$ - or  $\beta$ -acyloxy group derived from a monocarboxylic acid containing from 1 to 10 carbon atoms, or an  $\alpha$ - or  $\beta$ -acid acyloxy group derived from a polycarboxylic acid containing from 2 to 8 carbon atoms, and the alkali-metal, ammonium and substituted ammonium salts of these polycarboxylic acid esters, and

Y represents an oxo- or  $\beta$ -hydroxyl group, is combined with a pharmaceutical carrier which is inert to the active substituent, harmless to human beings, and suitable for oral or parenteral administration.

2. Process according to claim 1, characterised in that an alkali metal, ammonium or substituted ammonium salt of an acid ester of a lower aliphatic dicarboxylic acid containing 2 to 8 carbon atoms is used.

3. Process according to claim 2, characterised in that an alkali metal, ammonium or substituted ammonium salt of the acid ester of succinic acid is used.

4. Process for the preparation of new water soluble compounds of the pregnane series, applied in the processes according to claims 1—3, which compounds have a depressor effect on the central nervous system, characterised in that a pregnane or allopregnane compound of the formula:



wherein Y representing an oxo- or  $\beta$ -hydroxyl group is allowed to react with the required polycarboxylic acid or the anhydride thereof and the resulting acid ester is converted into an alkali metal, ammonium or substituted ammonium salt.

5. Process according to claim 4, characterised in that the esterification is carried out with a lower aliphatic dicarboxylic acid containing 2—8 carbon atoms.

6. Process according to claim 5, characterised in that the esterification is carried out with succinic acid anhydride.

7. Process according to one or more of the claims 4—6, characterised in that as starting product is applied:  $3\alpha$ -hydroxy-11:20-dioxo-pregnane.

8. Process according to one or more of the claims 4—6, characterised in that as starting product is applied:  $3\alpha$ -hydroxy-11:20-dioxo-allopregnane.

9. Process according to one or more of the claims 4—6, characterised in that as starting product is applied:  $3\beta$ -hydroxy-11:20-dioxo-allopregnane.

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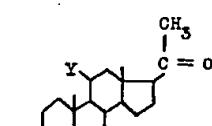
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10. Process according to one or more of the claims 4—6, characterised in that as starting product is applied:  $3\alpha$ :11 $\beta$ -dihydroxy-20-oxo-pregnane.

5 11. Process according to one or more of the claims 4—6, characterised in that as starting product is applied:  $3\beta$ :11 $\beta$ -dihydroxy-20-oxo-pregnane.

10 12. A 3-acid polycarboxylic ester of a pregnane or allopregnane compound of the formula:


  
 wherein Y represents an oxo- or 11 $\beta$ -hydroxyl group in which the polycarboxylic acid has 2—8 carbon atoms.

15 13. A 3-acid ester of a lower aliphatic dicarboxylic acid containing 2—8 carbon atoms and a pregnane or allopregnane compound of the formula according to claim 12.

20 14. A 3-acid succinic ester of a pregnane or allopregnane compound of the formula according to claim 12.

15 15. An alkali metal, ammonium, or substituted ammonium salt of a 3-acid polycarboxylic ester of a pregnane or allopregnane compound of the formula according to claim

25 12 in which the polycarboxylic acid contains 2—8 carbon atoms.

16. An alkali metal, ammonium, or substituted ammonium salt of a 3-acid ester of a lower aliphatic dicarboxylic acid with 2—8 carbon atoms and a pregnane or allopregnane compound of the formula according to claim 12.

30 17. An alkali metal, ammonium, or substituted ammonium salt of a 3-acid succinic ester and a pregnane or allopregnane compound of the formula according to claim 12.

35 18. An alkali metal, ammonium or substituted ammonium salt of a 3-acid polycarboxylic ester of

$3\alpha$ -hydroxy-11:20-dioxo-pregnane;  
 $3\alpha$ -hydroxy-11:20-dioxo-allopregnane;  
 $3\beta$ -hydroxy-11:20-dioxo-allopregnane;  
 $3\alpha$ :11 $\beta$ -dihydroxy-20-oxo-pregnane; or  
 $3\beta$ :11 $\beta$ -dihydroxy-20-oxo-pregnane,  
 in which the polycarboxylic acid contains 2—8 carbon atoms.

40 19. The sodium salt of the 3-hemisuccinate of

$3\alpha$ -hydroxy-11:20-dioxo-pregnane;  
 $3\alpha$ -hydroxy-11:20-dioxo-allopregnane;  
 $3\beta$ -hydroxy-11:20-dioxo-allopregnane;  
 $3\alpha$ :11 $\beta$ -dihydroxy-20-oxo-pregnane; or  
 $3\beta$ :11 $\beta$ -dihydroxy-20-oxo-pregnane.

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